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Whole exome sequencing unravels new genes associated with mitral valve prolapse

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Background: Several studies have suggested a familial clustering of mitral valve prolapse (MVP), especially for Barlow disease (BD), which is regarded as the effect of genetic or developmental errors. However, the genetic etiology of MVP, in particular BD, is largely unknown. So far only three genes have been identified: FLNA, DCHS1 and PLD1.
Purpose: The aim of this study was to identify genes associated with MVP using whole exome sequencing (WES).
Methods: Patients with MVP, who were classified as BD and/or had a positive family history for MVP, were referred for genetic counseling and WES. In total, 106 unrelated probands were included to identify potentially pathogenic variants in a set of 551 genes associated with cardiovascular development and/or diseases. The population databases Genome Aggregation and WES data from 110 parents of children with mental retardation were used as controls. Variants were analyzed using prediction programs, frequency in the population database and literature search. Variants were divided into the following categories: likely benign, variant of unknown significance or likely pathogenic.
Results: Thirteen percent (14/106) of the probands had a likely pathogenic variant in seven different genes: DCHS1 (1x), DSP (1x), HCN4 (2x), MYH6 (1x), TMEM67 (1x), TRPS1 (1x) and TTN (7x); the DSP, MYH6 and HCN4 variants cosegregated in affected relatives. None of the 110 parents of children with mental retardation had a likely pathogenic variant in these seven genes. In addition, 31% (33/106) of the probands harbored a variant of unknown significance in 23 different genes, including the genes DSP, FLNA, MYH6 and TTN (Fig). Remarkable, one variant of unknown significance in the FBN2 gene was shared among three unrelated probands and did not occur in population databases.
Conclusion: WES analysis conducted in probands with MVP using a large panel of genes associated with cardiac development and/or disease confirmed previously known causative genes (DCHS1) and expanded the cardiac phenotype of genes originally associated with cardiomyopathy (DSP, HCN4, MYH6 and TTN). This study is the first study that described the association between MVP and the genes DSP, MYH6 and TTN although the pathogenesis is still unknown. This high yield of likely pathogenic variants emphasizes the importance of genetic screening in MVP patients.